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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,823	02/12/2002	Waldemar Debinski	6460-41	8785

7590 06/04/2007

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
06/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/075,823	DEBINSKI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/19/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 9-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-14 and 18-43 are pending.

2. Claims 3-8 and 19-43 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 3/19/07, the following rejection remains.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-2, 9-14 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Takano et al (Cancer Research 56: 285-2190, May 1996; PTO 1449) as evidence by Amalfitano et al (of record, Cancer Genet Cytogenet 116: 6-9, 2000; PTO 892) in view of Achen et al (Eur J Biochem 267: 2505-2515, 2000; PTO 1449) and US Pat No. 6,235,713 B1 (of record, filed Aug 1997; PTO 892).

Takano et al teach a method for detecting glioblastoma multiforme in a brain tissue sample from human patients (see entire document, page 2185, col. 2, Materials and Methods, in particular). The reference method comprises the step of providing a brain tissue sample from brain tumor tissues and a sample from normal brain tissues (see page 2185, Col. 2, Tissue

preparation, in particular), contacting the brain tissue sample with an antibody such as monoclonal antibody MV303 or polyclonal antibody that binds specifically to human $VEGF_{121}$ (see page 2185, col. 2, Immunocytochemistry, VEGF ELISA, in particular), detecting the overexpression of $VEGF_{121}$ in brain tissue (see page 2187, Fig. 2, in particular) and correlating the overexpression of $VEGF_{121}$ in tumor brain tissue with glioblastoma multiforme (see paragraph bridging page 2186 and 2187, Fig. 2A vs. Fig. 2E, Fig. 1, in particular). Takano et al also teach comparing the quantity of expression of VEGF121 with a sample known to express detectable levels of VEGF such as menigioma (positive control) and a sample known not to express detectable levels of the $VEGF_{121}$ such as normal brain tissue (negative control) (see page 2186, Table 1, Fig. 1, in particular). Takano et al teach VEGF is a useful maker and measurable elements of glioblastoma angiogenesis; it is possible that measurement of VEGF and other angiogenic peptides in tissue together with the measurement of neovascularization in the brain tumor itself, may be used to improve the management of patients with brain tumors (see abstract, page 2189, col. 2, last paragraph, in particular). As evidence by the teachings of Amalfitano et al teach that glioblastoma multiforme cell exhibited abnormal ploidy for chromosome X (see page 6, col. 1, in particular).

The claimed invention differs from the teachings of the references only in that the method of detecting wherein the antibody is labeled and binds specifically to human VEGF-D protein, or a native human VEGF-D protein or homology domain of human VEGF-D instead of $VEGF_{121}$.

Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that bind specifically to fully processed bioactive homology domain (VHD) of human VEGF-D (VEGF-DΔNΔC), which is a proteolytic cleavage product (see entire document, paragraph bridging pages 2508-2509, in particular). All four of the reference mAbs also bind to the full-length unprocessed (native) human VEGF-D, especially mAb VD1 (see page 2508, col. 2, page 2505, col.1, last paragraph, in particular). Achen et al teach VEGF-D contributes to the development of blood vessels and lymphatic vessels during tumor growth (see page 2505, col. 2, last paragraph, in particular). Achen et al teach antibodies to VEGF-D will be powerful tools for analysis of the biological functions of VEGF-D and its role in VEGF-D in tumor angiogenesis as well as other inappropriate angiogenesis (see abstract, page 2513, col. 1 second and third paragraphs, in particular).

The '713 patent teaches a method of detecting VEGF-D in a biological sample comprising the steps of contacting a sample with a probe such as labeled polyclonal or

monoclonal that binds specifically to human VEGF-D (see col. 5, lines 56-67, col. 6, lines 1-10, col. 6, lines 66-67 bridging col. 7, lines 1-7, in particular). The reference VEGF-D is a native VEGF-D protein (see col. 19, lines 34-42, VEGFD full FLAG, in particular) and could be proteolytic cleaved to form the VEGF-D homology domain (see col. 19, line 25, VEGFDΔNΔC, in particular). The '713 patent teaches VEGF-D is located on the X chromosome in band p22.1 (see col. 24, lines 1-8, in particular) and is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular). The '713 patent further teaches a method of detecting the aberrations in VEGF-D located on the X chromosome (see col. 7, lines 40-43, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect glioblastoma multiforme from brain tissue sample as taught by Takano by substituting the monoclonal or polyclonal antibody that binds to $VEGF_{121}$ as taught by Takano et al for the labeled monoclonal antibody such as VD1 that binds to human VEGF-D protein, or a native human VEGF-D protein (full-length) or homology domain of human VEGF-D (processed) as taught by Achen et al or the polyclonal or monoclonal antibody that binds to the human VEGF-D as taught by the '713 patent where glioblastoma multiforme cells are known to exhibit abnormal ploidy for chromosome X as taught by Amalfitano et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Takano et al teach VEGF is a useful maker for glioblastoma multiforme (GBM) angiogenesis (see abstract, page 2189, col. 2, last paragraph, in particular) and known to exhibited abnormal ploidy for chromosome X as taught by Amalfitano et al. Achen et al teach antibodies to VEGF-D will be powerful tools for analysis of the biological functions of VEGF-D and its role in tumor angiogenesis as well as other inappropriate angiogenesis (see abstract, page 2513, col. 1 second and third paragraphs, in particular). The '713 patent teaches VEGF-D is located on the X chromosome in band p22.1 (see col. 24, lines 1-8, in particular) and VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and VEGF-D detection using antibody is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

Applicants' arguments filed 3/19/07 have been fully considered but are not found persuasive.

Applicants' position is that Takano et al., discuss VEGF in the sera and tumor extracts of patients. Takano et al., indicate that VEGF121 is freely soluble and there appears to be poor cross reactivity between any other forms of VEGF. This shown in Figure 2 where the anaplastic astrocytoma also stained highly positive. (See, also Table 1). Applicants respectfully disagree with the Examiner's assertions that Takano et al., taken in view of Amalfitano et al, and Achen et al make the instant invention obvious. The highly cross-reactive antibody is by no means a method of identifying a glioblastoma as in the instant invention. The motivation does not exist in any of the cited to combine the references. As discussed, Takano et al., do not teach or disclose detection of VEGF-D by a labeled antibody in a brain sample. Amalfitano et al., do not teach the detection of full-length native VEGF-D in brain tissue samples. Achen et al, standing alone or in combination do not teach the detection of a native protein VEGF-D homology domain in brain cancer. None of the references teach the detection of VEGF-D in the brain nor, was the form of VEGF-D in the brain known prior to applicants' invention. The motivation to combine these references is not provided by the references.

In response to applicants' argument that cross-reactive antibody as taught by Takano et al is by no means a method of identifying a glioblastoma as in the instant invention, Achen et al teach antibody that binds specifically to the native VEGF-D protein as well as antibody that binds specifically to the homology domain of VEGF-D. Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that bind specifically to fully processed bioactive homology domain (VHD) of human VEGF-D (VEGF-DΔNΔC), which is a proteolytic cleavage product (see entire document, paragraph bridging pages 2508-2509, in particular). All four of the reference mAbs also bind to the full-length unprocessed (native) human VEGF-D, especially mAb VD1 (see page 2508, col. 2, page 2505, col.1, last paragraph, in particular). In fact, the instant specification use the same antibody as taught by Achen et al (see page 32, line 2-30, in particular).

In contrast to applicants' assertion that there is no motivation to combine the references to arrive at the claimed invention, the combined teachings particularly Takano et al and Achen et al provide clear direction, motivation and expectation of success in detecting VEGF in brain tumor such as glioblastoma using antibody that binds specifically to VEGF-D or the homology domain of VEGF-D. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed

combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
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May 25, 2007

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